PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark Office, PCT
2011 South Clark Place Room CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 30 January 2001 (30.01.01)	
International application No. PCT/US00/06232	**Applicant's or agent's file reference** 204267
International filing date (day/month/year) 10 March 2000 (10.03.00)	**Priority date** (day/month/year) 10 March 1999 (10.03.99)
Applicant KATZ, Adam, J. et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

06 October 2000 (06.10.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer R. E. Stoffel
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/06232

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :Please See Extra Sheet.
US CL :424.93.1; 435/4, 320.1, 325, 366, 373, 455; 514/44
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424.93.1; 435/4, 320.1, 325, 366, 373, 455; 514/44

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

None

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Dialog and WEST

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X - Y	US 5,728,739 A (AILHAUD et al.) 17 March 1998, see especially the abstract, Background and summary.	1, 6-9 - 1-16, 39-48, 73-75 & 77-79
X - Y	US 5,827,897 A (AILHAUD et al.) 27 October 1998, see esecially the abstract, background and summary.	1 & 6-9 - 1-16, 39-48, 73-75 & 77-79
X - Y	US 5,827,740 A (PITTENGER) 27 October 1998, see especially the abstract, and columns 2-3	1 & 6-9 - 1-16, 39-48, 73-75 & 77-79

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 JUNE 2000	28 JUL 2000

Name and mailing address of the ISA/US	Authorized officer
Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	WILLIAM SANDALS
Facsimile No. (703) 305-3230	Telephone No. (703) 308-0196

Form PCT/ISA/210 (second sheet) (July 1998)★

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/06232

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5,486,359 A (CAPLAN et al.) 23 January 1996, see especially the abstract, columns 1-6 and 24-26.	1-16, 39-48, 73-75 & 77-79
X - Y	WO 98/04682 A1 (OSIRIS THERAPEUTICS, INC.) 05 February 1998, see especially the abstract, pages 1-8 & the claims.	1-4, 6-16, 39-48, 73-75 & 77-79 - 1-16, 39=48, 73-75 & 77-79
Y	CONSIDINE et al. Paracrine stimulation of preadipocyte-enriched cell cultures by mature adipocytes. American Journal of Physiology. May 1996, Vol. 270 (Endocinol. METAB. 33), E895-E899, see especially the abstract and the figures.	1-16, 39-48, 73-75 & 77-79
X - Y	SORISKY, A. From preadipocyte to adipocyte: Differentiation-directed signals of insulin from the cell surface to the nucleus. Critical Reviews in Clinical Laboratory Sciences. February 1999, Vol. 36, pages 1-34, see especially the abstract and pages 7-11.	1-3, 6-10, 12-16 - 1-16, 39-48, 73-75 & 77-79
Y	HUI-LING et al. Increased expression of G i alpha 2 in mouse embryo stem cells promotes terminal differentiation to adipocytes. Amerecan Journal of Physiology (Cell Physiology, 34). June 1993, Vol. 265, pages C1729-C1735, ses especially the abstract & discussion.	1-16, 39-48, 73-75 & 77-79
Y	YOUNG et al. Mesenchemal stem cells reside within the connective tissues of many organs. Developmental Dynamics. February 1995, Vol. 202, No. 2, pages 137-144, see especially the abstract, the figures and the tables.	1-16, 39-48, 73-75 & 77-79
Y	DANI et al. Differentiation of embryonic stem cells into adipocytes in vitro. Journal of Cell Science. June 1997, Vol. 110, pages 1279-1285, see especially the abstract, materials and methods and the figures.	1-16, 39-48, 73-75 & 77-79
Y	ESLAMI et al. Extracellular matrix components secreted by mivrovascular endothelial cells stimulate preadipocyte differentiation in vitro. Metabolism. July 1994, Vol. 43, No. 7, pages 906-912, see especially the abstract, the introduction and materials and methods.	1-16, 39-48, 73-75 & 77-79
Y	HAUNER et al. Endothelin-1 inhibits the adipose differentiation of cultured human adipocyte precursor cells. Metabolism. February 1994, Vol. 43, No, 2, pages 227-232, see especially the abstract, introduction and figures.	1-16, 39-48, 73-75, & 77-79

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/06232

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	MARKO et al. Isolation of a preadipocyte cell line from rat bone marrow and differentiation to adipocytes. Endocrinology. October 1995, Vol. 136, number 10, pages 4582-4588, see especially the abstract, introduction and figures.	1-16, 39-48, 73-75 & 77-79
Y	ENTENMANN et al. Relationship between replication and differentiation in cultured human adipocyte precursor cells. American Journal of Physiology (Cell Physiology, 39), APRIL 1996, Vol. 270, pages C1011-C1016, see especially the abstract, introduction and the figures.	1-16, 39-48, 73-75 & 77-79
Y	WABITSCH et al. Biological effectsof human growth hormone in rat adipocyte precursor cells and newly differentiated adipocytes in primary culture. METABOLISM, JANUARY 1996, Vol. 45, number 1, pages 34-42, see especially th abstract, introduction and figures.	1-16, 39-48, 73-75 & 77-79
Y	VASSAUX et al. Proloferation and differentiation of rat adipose precursor cells in chemically defined medium: Differential action of anti-adipogenic agents. Journal of Cellular Physiology. November 1994, Vol. 161, pages 249-256, see especially the abstract, introduction and figures.	1-16, 39-48, 73-75 & 77-79
Y	HAUSMAN et al. The influence of extracellular matrix substrata on preadipocyte develobment in serum-free cultures of stromal-vascular cells. Journal of Animal science. September 1996, Vol. 74, pages 2117-2128, see especially the abstract, introduction and discussion.	1-16, 39-48, 73-75 & 77-79
Y	SHILLABEER et al. A novel method for studying preadipocyte differentiation in vitro. International Journal of Obesity. March 1996, Vol. 20, Suppl. 3, pages S77-S83, see especially the abstract, introduction and figures.	1-16, 39-48, 73-75 & 77-79

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/06232

Box I- Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-16, 39-48, 73-75 & 77-79

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/06232

A. CLASSIFICATION OF SUBJECT MATTER:
IPC (7):

C12Q 1/00; C12N 5/00, 5/08, 15/63, 15/85; A01N 63/00; A61K 48/00

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I, claims 1-16, 39-48, 73-75 and 77-79, drawn to a lipoderived stem cell and a method of differentiating.
Group II, claims 17-25, drawn to a lipoderived lattice comprising extracellular matrix matter which contains no cells, and a kit drawn thereto.
Group III, claims 26-28, drawn to a composition comprising a cell and a lipoderived lattice.
Group IV, claims 29-35, drawn to a cell and a lipoderived lattice, where the lattice comprises polymeric material.
Group V, claims 36-37, drawn to a method of transfecting a lipoderived stem cell.
Group VI, claim 38, drawn to a method of gene therapy.
Group VII, claim 49, drawn to a method of producing hormones.
Group VIII, claim 50, drawn to a method of promoting wound closure by introducing a lipoderived stem cell which secretes a hormone.
Group IX, claims 51-54, drawn to a method of promoting neovascularization within a tissue by introducing a lipoderived stem which secretes a hormone.
Group X, claims 55-59, drawn to a method of conditioning culture medium with a lipoderived stem cell which secretes a hormone.
Group XI, claims 60-65, drawn to a method of culturing a stem cell in conditioned medium.
Group XII, claims 66-71 & 76 drawn to a method of growing and differentiating cells in a lipoderived lattice.
Group XIII, claim 72, drawn to a method of introducing into an animal a composition comprising a lipoderived lattice and a cell.
The inventions listed as Groups I and II do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: The stem cell of Group I is physically, biologically, biochemically and patentably distinct from the lattice of Group II.

The inventions listed as Groups I and III do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: The stem cell of Group I is physically, biologically, biochemically and patentably distinct from the cell which is grown and differentiated in a lattice.

The inventions listed as Groups I and IV do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: The stem cell of Group I is physically, biologically, biochemically and patentably distinct from the lattice comprised of polymeric material of Group IV.

The inventions listed as Groups I and V do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: The stem cell of Group I is physically, biologically, biochemically and patentably distinct from the method of transfecting a stem cell of Group V.

The inventions listed as Groups I and VI do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: The stem cell of Group I is physically, biologically, biochemically and patentably distinct from the method of gene therapy of Group VI.

The inventions listed as Groups I and VII do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: The stem cell of Group I is physically, biologically, biochemically and patentably distinct from the method of producing hormones of Group VII.

The inventions listed as Groups I and VIII do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: The

stem cell of Group I is physically, biologically, biochemically and patentably distinct from the method of promoting wound closure of Group VIII.

The inventions listed as Groups I and IX do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: The stem cell of Group I is physically, biologically, biochemically and patentably distinct from the method of neovascularization of Group IX.

The inventions listed as Groups I and X do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: The stem cell of Group I is physically, biologically, biochemically and patentably distinct from the composition and method of conditioning culture medium of Group X.

The inventions listed as Groups I and XI do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: The stem cell of Group I is physically, biologically, biochemically and patentably distinct from the method of culturing stem cells of Group XI.

The inventions listed as Groups I and XII do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: The stem cell of Group I is physically, biologically, biochemically and patentably distinct from the composition and method of producing animal matter of Group XII.

The inventions listed as Groups I and XIII do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: The stem cell of Group I is physically, biologically, biochemically and patentably distinct from the method of cell implant of Group XIII.

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under Article 19. The Notes are based on the requirements of the Patent Cooperation Treaty and of the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule" and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended ?

The claims only.

The description and the drawings may only be amended during international preliminary examination under Chapter II.

When ? Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments ?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been filed, see below.

How ? Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

What documents must/may accompany the amendments ?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confounded with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

(i) the claim is unchanged;
(ii) the claim is cancelled;
(iii) the claim is new;
(iv) the claim replaces one or more claims as filed;
(v) the claim is the result of the division of a claim as filed.

NOTES TO FORM PCT/ISA/220 (continued)

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under Article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

The statement should be brief, it should not exceed 500 words if in English or if translated into English.

It should not be confounded with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It should not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

In what language ?

The amendments must be made in the language in which the international application is published. The letter and any statement accompanying the amendments must be in the same language as the international application if that language is English or French; otherwise, it must be in English or French, at the choice of the applicant.

Consequence if a demand for international preliminary examination has already been filed ?

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase ?

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

PATENT COOPERATION TREATY

Dina

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To: HEFNER. M. DANIEL
LEYDIG. VOIT & MAYER. LTD.
TWO PRUDENTIAL PLAZA. SUITE 4900
180 NORTH STETSON
CHICAGO. ILLINOIS 60601-6780

PCT

WRITTEN OPINION

(PCT Rule 66)

Date of Mailing *(day/month/year)*	19 APR 2001
Applicant's or agent's file reference: 204267	REPLY DUE within ONE months from the above date of mailing

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US00/06232	10 MARCH 2000	10 MARCH 1999

International Patent Classification (IPC) or both national classification and IPC
Please See Supplemental Sheet.

Applicant
UNIVERSITY OF PITTSBURGH OF THE COMMONWEALTH SYSTEM OF HIGHER EDUCATION

1. This written opinion is the first (first, etc.) drawn by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

- I [X] Basis of the opinion
- II [ ] Priority
- III [X] Non-establishment of opinion with regard to novelty, inventive step or industrial applicability
- IV [ ] Lack of unity of invention
- V [X] Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI [ ] Certain documents cited
- VII [ ] Certain defects in the international application
- VIII [ ] Certain observations on the international application

LEYDIG, VOIT & MAYER
RECEIVED
APR 23 2001
PAT/TM Due Date 5-19-01

3. The applicant is hereby invited to reply to this opinion.

When? See the time limit indicated above. ~~The applicant may, before the expiration of that time limit, request this Authority to grant an extension., see Rule 66.2(d).~~

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 *bis*.
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 10 JULY 2001

Name and mailing address of the IPEA/US	Authorized officer
Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Dorothea Faulkner for WILLIAM SANDALS DNG
Facsimile No. (703) 305-3230	Telephone No. (703) 308-0196

LH

Form PCT/IPEA/408 (cover sheet) (July 1998)*

WRITTEN OPINION

International application No.
PCT/US00/06232

I. Basis of the opinion

1. With regard to the elements of the international application:*

[X] the international application as originally filed

[X] the description:
pages 1-23 , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

[X] the claims:
pages 24-29 , as originally filed
pages NONE , as amended (together with any statement) under Article 19
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

[X] the drawings:
pages NONE , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

[X] the sequence listing part of the description:
pages NONE , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

[ ] the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

[ ] the language of publication of the international application (under Rule 48.3(b)).

[ ] the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the written opinion was drawn on the basis of the sequence listing:

[ ] contained in the international application in printed form.

[ ] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readable form.

[ ] The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] The statement that the information recorded in computer readable form is identical to the writen sequence listing has been furnished.

4. [X] The amendments have resulted in the cancellation of:

[X] the description, pages None

[X] the claims, Nos. None

[X] the drawings, sheets/~~fig~~ None

5. [X] This opinion has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed".*

WRITTEN OPINION

International application No.
PCT-US00-06232

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been and will not be examined in respect of:

☐ the entire international application.

☒ claims Nos. 17-38, 49-72, 76

because:

☐ the said international application, or the said claim Nos. _ relate to the following subject matter which does not require international preliminary examination *(specify)*.

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 5-14, 20-76 are so unclear that no meaningful opinion could be formed *(specify)*.

These claims have not been drafted to meet the requirements set forth under PCT RULE 6.4(a). The claims are multiply dependent and as such are unclear such that no meaningful opinion can be formed.

☐ the claims, or said claims Nos. _ are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for said claims Nos. 17-38, 49-72, 76.

2. A written opinion cannot be drawn due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

WRITTEN OPINION

International application No.
PCT US00/06232

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. statement

Novelty (N)	Claims	None	YES
	Claims	1-4, 15-16, 77-79	NO
Inventive Step (IS)	Claims	None	YES
	Claims	1-4, 15-16, 77-79	NO
Industrial Applicability (IA)	Claims	1-4, 15-16, 77-79	YES
	Claims	None	NO

2. citations and explanations

Claims 1-4, 15-16, 77-79 lack novelty under PCT Article 33(2) as being anticipated by each of US 5,486,359 or WO 98/04682.

Each of US 5,486,359 taught or WO 98/04682 taught a human lipo-derived stem cell which was homogeneous and substantially free of mature adipocytes where the stem cells were cultured for at least 15 passages and had two or more developmental phenotypes. The stem cells may be genetically modified, may secrete hormones, may have cell surface receptors. The stem cells may be induced to differentiate into mature cells (ie. adipocytes, myocytes, neural cells, etc.) by specific culture media or in vivo conditions. The cells may be used for implantation. Kits for isolation, and culturing may be provided.

Claims 1, 2 15 and 16 lack novelty under PCT Article 33(2) as being anticipated by each of Dodson et al. or Marko et al. or Dani et al. or Young et al. or Hui-ling Su et al.

Each of Dodson et al. or Marko et al. or Dani et al. or Young et al. or Hui-ling Su et al. taught a mammalian lipo-derived stem cell which was homogeneous and substantially free of mature adipocytes where the stem cells were cultured for at least 15 passages.

Claims 1, 15 lack novelty under PCT Article 33(2) as being anticipated by each of US 5,728, 739 or US 5827,897 or US 5,827,740.

Each of US 5,728, 739 or US 5827,897 or US 5,827,740 taught a mammalian lipo-derived stem cell which was homogeneous and substantially free of mature adipocytes which may have cell surface receptors. The cells may be used for implantation.

Claims 1-3, 15, 16 lack novelty under PCT Article 33(2) as being anticipated by Sorisky et al.

(Continued on Supplemental Sheet.)

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

TIME LIMIT:

The time limit set for response to a Written Opinion may not be extended. 37 CFR 1.484(d). Any response received after the expiration of the time limit set in the Written Opinion will not be considered in preparing the International Preliminary Examination Report.

CLASSIFICATION:

The International Patent Classification (IPC) and/or the National classification are as listed below:
IPC(7): C12Q 1/00; C12N 5/00, 5/08, 15/63, 15/85; A01N 63/00; A61K 48/00 and US Cl.: 424.93.1; 435/4, 320.1, 325, 366, 373, 455; 514/44

I. BASIS OF OPINION:

5. (Some) amendments are considered to go beyond the disclosure as filed:
None

V. 2. REASONED STATEMENTS - CITATIONS AND EXPLANATIONS (Continued):

Sorisky et al. taught a mammalian lipo-derived stem cell which was homogeneous and substantially free of mature adipocytes where the stem cells were cultured for at least 15 passages and had two or more developmental phenotypes. The stem cells may secrete hormones, may have cell surface receptors. The stem cells may be induced to differentiate into mature cells (ie. adipocytes, myocytes, neural cells, etc.) by specific culture media or in vivo conditions.

Claims 1-4, 15-16, 77-79 lack an inventive step under PCT Article 33(3) as being obvious over each of US 5,486,359 or WO 98/04682 or Dodson et al. or Marko et al. or Dani et al. or Young et al. or Hui-ling Su et al. or US 5,728, 739 or US 5827,897 or US 5,827,740 or Sorisky et al. in view of each of Hausman et al. or Shillabeer et al. or Vassaux et al. or Hauner et al. or Considine et al.

Each of US 5,486,359 or WO 98/04682 or Dodson et al. or Marko et al. or Dani et al. or Young et al. or Hui-ling Su et al. or US 5,728, 739 or US 5827,897 or US 5,827,740 or Sorisky et al. taught the claimed invention as in the lack of novelty rejections above. Hausman et al. taught an extracellular matrix which enhanced stem cells to mature into adipocytes. Shillabeer et al. taught the use of conditioned medium to induce stem cells into adipocytes. Vassaux et al. taught hormone and cytokine induction of stem cells to produce adipocytes. Hauner et al. taught the use of a hormone to induce stem cells to mature into adipocytes. Considine et al. taught that genetically modified stem cell may be induced by exposure to hormone or cytokine to produce mature adipocytes.

It would have been obvious to one of ordinary skill in the art at the time of filing of the instant invention to combine the teachings of US 5,486,359 or WO 98/04682 or Dodson et al. or Marko et al. or Dani et al. or Young et al. or Hui-ling Su et al. or US 5,728, 739 or US 5827,897 or US 5,827,740 or Sorisky et al. with each of Hausman et al. or Shillabeer et al. or Vassaux et al. or Hauner et al. or Considine et al. because they were all studying the effects of growth and maturation factors on the induction of stem cells to mature into a defined mature phenotype such as adipocytes.

One of ordinary skill in the art would have been motivated at the time of filing of the instant invention to combine the teachings of US 5,486,359 or WO 98/04682 or Dodson et al. or Marko et al. or Dani et al. or Young et al. or Hui-ling Su et al. or US 5,728, 739 or US 5827,897 or US 5,827,740 or Sorisky et al. with each of Hausman et al. or Shillabeer et al. or Vassaux et al. or Hauner et al. or Considine et al. because US 5,486,359 states in the abstract "[i]solated human mesenchymal stem cells which can differentiate into more than one tissue type (e.g. bone, cartilage, muscle or marrow stroma), a method for isolating, purifying, and culturally expanding human mesenchymal stem cells (e.e. 'mesenchymal stem cells' or 'hMSCs') and characterization of and uses, particulary research reagent, diagnostic and therapeutic uses for such cells. The cells can be culture expanded without differentiating". This is followed at column 1, lines 22-30, "[m]esenchymal stem cells are the formative pluripotential blast cells found inter alia in bone marrow, blood, dermis and periosteum that are capable of differentiating into any of the specific types of mesenchymal or connective tissues (i.e. the tissues of the body that support the specialized elements; particularly adipose, osseous, cartilaginous, elastic, and fibrous connective tissues) depending upon various influences from bioactive factors, such as cytokines". Further, a person of ordinary skill in the art would have had a reasonable expectation of success in producing the instant claimed invention given the teachings of US 5,486,359 or WO 98/04682 or Dodson et al. or Marko et al. or Dani et al. or Young et al. or Hui-ling Su et al. or US 5,728, 739 or US 5827,897 or US 5,827,740 or Sorisky et al. with each of Hausman et al. or Shillabeer et al. or Vassaux et al. or Hauner et al.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

or Considine et al.

---------- NEW CITATIONS ----------

DODSON et al. The Development and Utility of a Defined Muscle and Fat co-culture System. Tissue and Cell. September 1997, Vol. 29, No. 5, pages 517-524, see especially pages 517-519.

Agent's reference 204267

In the IPEA/US

International Appl'n No. PCT/US00/06232	International filing date *(day/month/year)* 10 MARCH 2000 (10.03.00)	(Earliest) Priority date *(day/month/year)* 10 MARCH 1999 (10.03.99)
Title of invention ADIPOSE-DERIVED STEM CELLS AND LATTICES		
Applicant(s) UNIVERSITY OF PITTSBURGH OF THE COMMONWEALTH SYSTEM OF HIGHER EDUCATION et al.		

Response to Written Opinion

Commissioner of Patents and Trademarks
BOX PCT
Washington, D.C. 20231

Attn: William Sandals

Dear Mr. Sandals

In response to the Written Opinion, mailed on April 19, 2001, please consider the following remarks and enter the attached substitute sheets 28-32, replacing pages 28 and 29 of the application and serving to amend the claims.

Discussion of the Written Opinion

The Written Opinion has not been established with respect to claims 17-38, 49-72 and 76 because no international search report was generated with respect to these claims. Moreover, the opinion has not been established with respect to claims 5-14 or 20-76 because they are drafted in multiple-dependent form. With respect to claims that have been examined (i.e., claims 1-4, 15, 16, and 77-79), the Written Opinion alleges that all claims lack novelty in light of several references. Additionally, the Written Opinion alleges that the claims lack inventive step in light of any of these primary references in combination with several other secondary references.

Discussion of the Amendments

The application is amended to add claims 80-138. Claims 80-131 concern a lipo-derived stem cell substantially free of mature adipocytes, which can be cultured in DMEM + about 10% fetal bovine serum without differentiating, and which has two or more identified developmental phenotypes, as well as populations of such cells and methods of using such cells. Such claims are supported in the specification, for example on page 2, lines 34-36, page 4, lines 35-37, and generally throughout the specification). Claims 132-138 concern a method of isolating stem cells from adipose tissue and are supported in the specification, for example, from page 3, line 24, through page 4, line 2; see also Example 1. Accordingly, these claims add no new matter to the application.

Discussion of Novelty

The Written Opinion alleges that claims 1-4, 15, 16, and 77-79 lack novelty in light of eleven references, as follows:

Reference	Claims
Dani et al.	1, 2, 15, 16
Dodson et al.	1, 2, 15, 16
Hui-ling Su et al.	1, 2, 15, 16
Marko et al.	1, 2, 15, 16
Sorisky et al.	1-3, 15, 16
U.S. Patent 5,486,359	1-4, 15-16, 77-79
U.S. Patent 5,728,739	1, 15
U.S. Patent 5,827,740	1, 15
U.S. Patent 5,827,897	1, 15
WO 98/04682	1-4, 15-16, 77-79
Young et al.	1, 2, 15, 16

Claim 1 is drawn to a "lipo-derived stem cell," and each of the other rejected claims depends from claim 1. As stated in the specification, a "lipo-derived stem cell" is a stem cell that is isolated from adipose tissue (see, e.g., page 3, lines 24-32). A "stem cell," in turn, is a cell that has the capacity to develop into at least two discrete developmental pathways (see page 23, lines 5-6). Thus, for any reference to anticipate the claims, such reference must disclose a cell that has the capacity to develop into at least two discrete developmental pathways that is isolated from adipose tissue. None of the references disclose such subject matter. Instead, the references disclose the following:

Reference	Disclosure
Dani et al.	Discloses isolation of embryonic stem cells from undifferentiated blastocysts (see page 1279, column 2). Obviously, at such an early developmental stage, no adipose tissue has formed. Thus, the stem cells isolated by Dani ***could not possibly be lipo-derived***.
Dodson et al.	Disclosed a muscle/fat co-culture system and the differentiation of satellite cells. Such cells are ***not lipo-derived*** because they are derived from muscle tissue. Moreover, satellite cells are ***not stem cells*** because they are predetermined precursor cells (see, e.g., Young et al., page 202, column 2).
Hui-ling Su et al.	Discloses experiments conducted using embryonic mouse fibroblasts, ***not stem cells***
Marko et al.	A cell line isolated from bone marrow, ***not lipo-derived***
Sorisky et al.	Discloses the differentiation of preadipocytes. The document notes that preadipocytes are "committed to adipocyte lineage" (e.g., page 10, Fig 1); therefore such cells are ***not stem cells***.

Reference	Disclosure
U.S. Patent 5,486,359	Stem cells obtained from bone marrow, blood, dermis, periosteum, yolk sac, placenta, or umbilical cord (see column 1, lines 22-34, column 2, lines 18-21). As none of these tissues are adipose tissues, the stem cells described in this patent are ***not lipo derived***.
U.S. Patent 5,728,739 U.S. Patent 5,827,897	A method of differentiating preadipocytes, which are committed adipocyte precursor cells (see Sorisky et al., page 10) and therefore ***not stem cells***.
U.S. Patent 5,827,740 WO 98/04682	Discloses the differentiation of stem cells into adipose tissue. The stem cells, however, were derived from bone marrow and therefore ***not lipo-derived***.
Young et al.	Suggests the existence of stem cells in many embryonic tissues (see, e.g., table 1, page 139). The article does not identify adipose tissue as being one of those tissues, however. Thus, the article ***does not disclose lipo-derived stem cells***.

Thus, none of these references discloses the existence of stem cells within adipose tissue, nor do they disclose the isolation of stem cells from such tissue. As such, none of them discloses the subject matter of claim 1, nor any claims dependent thereon.

Discussion of Inventive Step

The Office Action alleges that claims 1-4, 15-16, and 77-79 lack an inventive step in light of the primary references discussed above in combination with either Considine et al., Hauner et al., Hausman et al., Shillabeer et al., or Vassaux et al. As is the case with respect to the primary references, none of these secondary references discloses a stem cell isolated or derived from adipose tissue. Thus, none of the cited references, alone or in combination, places the inventive lipo-derived stem cells within the state of the art. As such, the claims are inventive in light of all cited references.

Conclusion

The application is considered to be in good and proper form, and the Examiner is respectfully urged to indicate the acceptability of the present patent application in the International Preliminary Examination Report. If, in the opinion of the Examiner, a telephone conference would be of assistance in considering the subject application, the Examiner is invited to contact the undersigned by telephone.

Respectfully submitted,

M. Daniel Hefner
One of the Agents for Applicants
LEYDIG, VOIT & MAYER, LTD.
Two Prudential Plaza, Suite 4900
180 North Stetson St.
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Date: 18 May, 2001

Substitute sheets follow

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

14

Applicant's or agent's file reference 204267	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US00/06232	International filing date *(day/month/year)* 10 MARCH 2000	Priority date *(day/month/year)* 10 MARCH 1999
International Patent Classification (IPC) or national classification and IPC Please See Supplemental Sheet.		
Applicant UNIVERSITY OF PITTSBURGH OF THE COMMONWEALTH SYSTEM OF HIGHER EDUCATION		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets.

   [V] This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 4 sheets.

3. This report contains indications relating to the following items:

   I [X] Basis of the report

   II [ ] Priority

   III [X] Non-establishment of report with regard to novelty, inventive step or industrial applicability

   IV [ ] Lack of unity of invention

   V [X] Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

   VI [ ] Certain documents cited

   VII [ ] Certain defects in the international application

   VIII [ ] Certain observations on the international application

Date of submission of the demand	Date of completion of this report
06 OCTOBER 2000	29 JUNE 2001
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer Dorthea Lawrence for WILLIAM SANDALS Telephone No. (703) 308-0196

Form PCT/IPEA/409 (cover sheet) (July 1998) ★

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US00/06232

I. Basis of the report

1. With regard to the **elements** of the international application:*

☐ the international application as originally filed

☒ the description:
pages (See Attached), as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

☒ the claims:
pages (See Attached), as originally filed
pages _____, as amended (together with any statement) under Article 19
pages _____, filed with the demand
pages _____, filed with the letter of _____

☒ the drawings:
pages (See Attached), as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

☒ the sequence listing part of the description:
pages (See Attached), as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in printed form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the writen sequence listing has been furnished.

4. ☒ The amendments have resulted in the cancellation of:

☒ the description, pages None

☒ the claims. Nos. 62-78

☒ the drawings. sheets~~fig~~ None

5. ☒ This report has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed. as indicated in the Supplemental Box (Rule 70.2(c)).**

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

***Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been and will not be examined in respect of:

☐ the entire international application.

☒ claims Nos. 5-14, 17-61, 83-86, 88, 93-138

because:

☐ the said international application, or the said claim Nos. _ relate to the following subject matter which does not require international preliminary examination *(specify)*.

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 5-14, 39-61 are so unclear that no meaningful opinion could be formed *(specify)*.

These claims have not been drafted to meet the requirements set forth under PCT RULE 6.4(a). The claims are multiply dependent and as such are unclear such that no meaningful opinion can be formed.

☐ the claims, or said claims Nos _ are so inadequately supported by the description that no meaningful opinion could be formed

☒ no international search report has been established for said claims Nos. (See Attached) .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. statement

Novelty (N)	Claims	87, 89-92	YES
	Claims	1-4, 15-16, 79	NO
Inventive Step (IS)	Claims	NONE	YES
	Claims	1-4, 15-16, 79-82, 87, 89-92	NO
Industrial Applicability (IA)	Claims	1-4, 15-16, 79-82, 87, 89-92	YES
	Claims	NONE	NO

2. citations and explanations (Rule 70.7)

Claims 1-4, 15-16, 79 lack novelty under PCT Article 33(2) as being anticipated by each of US 5,486,359 or WO 98/04682.

Each of US 5,486,359 taught or WO 98/04682 taught a human lipo-derived stem cell which was homogeneous and substantially free of mature adipocytes where the stem cells were cultured for at least 15 passages and had two or more developmental phenotypes. The stem cells may be genetically modified, may secrete hormones, may have cell surface receptors. The stem cells may be induced to differentiate into mature cells (ie. adipocytes, myocytes, neural cells, etc.) by specific culture media or in vivo conditions. The cells may be used for implantation. Kits for isolation, and culturing may be provided.

Claims 1, 2 15 and 16 lack novelty under PCT Article 33(2) as being anticipated by each of Dodson et al. or Marko et al. or Dani et al. or Young et al. or Hui-ling Su et al.

Each of Dodson et al. or Marko et al. or Dani et al. or Young et al. or Hui-ling Su et al. taught a mammalian lipo-derived stem cell which was homogeneous and substantially free of mature adipocytes where the stem cells were cultured f or at least 15 passages.

Claims 1, 15 lack novelty under PCT Article 33(2) as being anticipated by each of US 5,728, 739 or US 5827,897 or US 5,827,740.

Each of US 5,728, 739 or US 5827,897 or US 5,827,740 taught a mammalian lipo-derived stem cell which was homogeneous and substantially free of mature adipocytes which may have cell surface receptors. The cells may be used for implantation.

Claims 1-3, 15, 16 lack novelty under PCT Article 33(2) as being anticipated by Sorisky et al.

(Continued on Supplemental Sheet.)

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

CLASSIFICATION:
The International Patent Classification (IPC) and/or the National classification are as listed below:
IPC(7): C12Q 1/00; C12N 5/00, 5/08, 15/63, 15/85; A01N 63/00; A61K 48/00 and US Cl.: 424.93.1; 435/4, 320.1, 325, 366, 373, 455; 514/44

I. BASIS OF REPORT:

This report has been drawn on the basis of the description,
page(s) 1-23, as originally filed.
page(s) NONE, filed with the demand.
and additional amendments:
NONE

This report has been drawn on the basis of the claims,
page(s) 24-27, as originally filed.
page(s) NONE, as amended under Article 19.
page(s) NONE, filed with the demand.
and additional amendments:
Pages 28-31, filed with the letter of 18 MAY 2001.

This report has been drawn on the basis of the drawings,
page(s) NONE, as originally filed.
page(s) NONE, filed with the demand.
and additional amendments:
NONE

This report has been drawn on the basis of the sequence listing part of the description:
page(s) NONE, as originally filed.
pages(s) NONE, filed with the demand.
and additional amendments:
NONE

5. (Some) amendments are considered to go beyond the disclosure as filed:
None

III. NON-ESTABLISHMENT OF REPORT:

No international search report has been established for claim numbers 17-38, 49-61, 83-86, 88, 93-138 Claims 83-86, 88 and 93-138 are drawn to non-elected invention which were not searched in chapter 1. As such, they were not examined in this report.

V. 2. REASONED STATEMENTS - CITATIONS AND EXPLANATIONS (Continued):

Sorisky et al. taught a mammalian lipo-derived stem cell which was homogeneous and substantially free of mature adipocytes where the stem cells were cultured for at least 15 passages and had two or more developmental phenotypes. The stem cells may secrete hormones, may have cell surface receptors. The stem cells may be induced to differentiate into mature cells (ie. adipocytes, myocytes, neural cells, etc.) by specific culture media or in vivo conditions.

Claims 1-4, 15-16, 79-82, 87, 89-92 lack an inventive step under PCT Article 33(3) as being obvious over each of US 5,486,359 or WO 98/04682 or Dodson et al. or Marko et al. or Dani et al. or Young et al. or Hui-ling Su et al. or US 5,728, 739 or US 5827,897 or US 5,827,740 or Sorisky et al. in view of each of Hausman et al. or Shillabeer et al. or Vassaux et al. or Hauner et al. or Considine et al.

Each of US 5,486,359 or WO 98/04682 or Dodson et al. or Marko et al. or Dani et al. or Young et al. or Hui-ling Su et al. or US 5,728, 739 or US 5827,897 or US 5,827,740 or Sorisky et al. taught the claimed invention as in the lack of

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

novelty rejections above. Hausman et al. taught an extracellular matrix which enhanced stem cells to mature into adipocytes. Shillabeer et al. taught the use of conditioned medium to induce stem cells into adipocytes. Vassaux et al. taught hormone and cytokine induction of stem cells to produce adipocytes. Hauner et al. taught the use of a hormone to induce stem cells to mature into adipocytes. Considine et al. taught that genetically modified stem cell may be induced by exposure to hormone or cytokine to produce mature adipocytes.

It would have been obvious to one of ordinary skill in the art at the time of filing of the instant invention to combine the teachings of US 5,486,359 or WO 98/04682 or Dodson et al. or Marko et al. or Dani et al. or Young et al. or Hui-ling Su et al. or US 5,728, 739 or US 5827,897 or US 5,827,740 or Sorisky et al. with each of Hausman et al. or Shillabeer et al. or Vassaux et al. or Hauner et al. or Considine et al. because they were all studying the effects of growth and maturation factors on the induction of stem cells to mature into a defined mature phenotype such as adipocytes.

One of ordinary skill in the art would have been motivated at the time of filing of the instant invention to combine the teachings of US 5,486,359 or WO 98/04682 or Dodson et al. or Marko et al. or Dani et al. or Young et al. or Hui-ling Su et al. or US 5,728, 739 or US 5827,897 or US 5,827,740 or Sorisky et al. with each of Hausman et al. or Shillabeer et al. or Vassaux et al. or Hauner et al. or Considine et al. because US 5,486,359 states in the abstract "[i]solated human mesenchymal stem cells which can differentiate into more than one tissue type (e.g. bone, cartilage, muscle or marrow stroma), a method for isolating, purifying, and culturally expanding human mesenchymal stem cells (e.e. 'mesenchymal stem cells' or 'hMSCs') and characterization of and uses, particulary research reagent, diagnostic and therapeutic uses for such cells. The cells can be culture expanded without differentiating". This is followed at column 1, lines 22-30, "[m]esenchymal stem cells are the formative pluripotential blast cells found inter alia in bone marrow, blood, dermis and periosteum that are capable of differentiating into any of the specific types of mesenchymal or connective tissues (i.e. the tissues of the body that support the specialized elements; particularly adipose, osseous, cartilaginous, elastic, and fibrous connective tissues) depending upon various influences from bioactive factors, such as cytokines". Further, a person of ordinary skill in the art would have had a reasonable expectation of success in producing the instant claimed invention given the teachings of US 5,486,359 or WO 98/04682 or Dodson et al. or Marko et al. or Dani et al. or Young et al. or Hui-ling Su et al. or US 5,728, 739 or US 5827,897 or US 5,827,740 or Sorisky et al. with each of Hausman et al. or Shillabeer et al. or Vassaux et al. or Hauner et al. or Considine et al.

Newly added claims 80-82, 87 and 89-92 have been included for examination with the previously examined group.

Newly added claims are drawn to a cell culture medium, and to cells from animal including human. These elements are taught by the references cited in the above rejection, and do not offer limitations which are free of the art.

The reply letter of 18 May 2001 stated that the Dani et al. reference did not teach lipo-derived stem cells. The instant specification at page 2, line 33 states that the instant claimed stem cells may be "any type of stem cell...of mesodermal origin". The cells of Dani et al. meet this requirement.

The reply letter of 18 May 2001 stated that the Dodson et al. reference taught the differentiation of satellite cells which are not stem cells, and that the cells of Dodson et al. were not lipo-derived. Dodson et al. at page 519, column 2, thrid paragraph taught that the stem cells were derived from "fat depots". The cells of Dodson et al. were from fat depots such as the lipo-derived cells of the instant claimed invention. Therefore, in the absence of evidence to the contrary, it must be assumed that the preadipocyte cells of Dodson et al. are the same as the instant claimed lipo-derived stem cells.

The reply letter of 18 May 2001 stated that the Su et al. reference taught embryonic mouse fibroblasts. Su et al. taught (see page C1729, column 2, middle, that the cells were 3T3-L1 cells. Dodson et al. taught that the 3T3-L1 cells are multipotent preadipocytes.

The reply letter of 18 May 2001 stated that the Marko et al. reference taught cells isolated from bone marrow, not fat. Bone marrow is known to be an abundant source of fat cells.

The reply letter of 18 May 2001 stated that the Sorisky et al. reference taught preadipocytes are "committed to adipocyte lineage at page 10, Fig. 1. Sorisky et al. is a review article. Sorisky et al. taught that a source of preadipocytes which were multipotent was available for study (see page 8).

The reply letter of 18 May 2001 stated that the US 5,486,359 reference taught cells derived from many sources (including bone marrow). As noted above, bone marrow is a known source of fat.

The reply letter of 18 May 2001 stated that the US 5,728,739 and US 5,827,897 references taught preadipocytes. As noted above in the reply to comments on Sorisky et al., Preadipocytes are multipotent stem cells.

The reply letter of 18 May 2001 stated that the US 5,827,740 and WO 98/04682 references taught preadipocytes. As noted above in the reply to comments on Sorisky et al., Preadipocytes are multipotent stem cells.

The reply letter of 18 May 2001 stated that the Young et al. reference did not teach lipo-derived stem cells. The instant specification at page 2, line 33 states that the instant claimed stem cells may be "any type of stem cell...of mesodermal origin". The cells of Young et al. meet this requirement.

Each of the above references anticipate the invention as stated in the lack of novelty, and the rebuttal offered in the letter of 18 May 2001 is not considered persuasive, for the foregoing reasons.

Rebuttal of the lack of inventive step is limited to a reference to the rebuttal of the lack of novelty above.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

Therefore, the rebuttal of the lack of inventive step is also not considered convincing for the reasons stated above.

---------- NEW CITATIONS ----------

DODSON et al. The Development and Utility of a Defined Muscle and Fat co-culture System. Tissue and Cell. September 1997, Vol. 29, No. 5, pages 517-524, see especially pages 517-519.

79. The kit of claim 78, wherein the medium is selected from the group of media consisting of adipogenic, chondrogenic, cardiogenic, dermatogenic, embryonic, fetal, hematopoetic, hemangiogenic, myogenic, nephrogenic, neurogenic, neuralgiagenic, urogenitogenic, osteogenic, pericardiogenic, peritoneogenic, pleurogenic, and splanchogenic, and stromogenic media.

80. A mammalian lipo-derived stem cell substantially free of mature adipocytes, which can be cultured in DMEM + about 10% fetal bovine serum without differentiating and which has two or more developmental phenotypes selected from the group of developmental phenotypes consisting of adipogenic, chondrogenic, cardiogenic, dermatogenic, hematopoetic, hemangiogenic, myogenic, nephrogenic, neurogenic, neuralgiagenic, urogenitogenic, osteogenic, pericardiogenic, peritoneogenic, pleurogenic, splanchogenic, and stromal developmental phenotypes.

81. The cell of claim 80, which can be cultured in DMEM + about 10% fetal bovine serum for at least 15 passages without differentiating

82. The cell of claim 80, which is human.

83. The cell of claim 80, which is genetically modified.

84. The cell of claim 80, which has a cell-surface bound intercellular signaling moiety.

85. The cell of claim 80, which secretes a hormone.

86. The cell of claim 85, wherein the hormone is selected from the group of hormones consisting of cytokines and growth factors.

87. A defined cell population comprising a cell of claim 80.

88. The defined cell population of claim 87, which is heterogeneous.

89. The defined cell population of claim 88, further compressing a stem cell selected from the group of cells consisting of neural stem cells (NSC), hematopoetic stem cells (HPC), embryonic stem cells (ESC) and mixtures thereof.

90. The defined cell population of claim 87, which consists essentially of cells according to claim 80.

91. The defined cell population of claim 87, which is substantially homogenous.

92. The defined cell population of claim 91, which is clonal.

93. A composition comprising the cell of claim 80 and a biologically compatible lattice.

94. A composition comprising the population of claim 87 and a biologically compatible lattice.

95. The composition of claim 94, wherein the lattice comprises polymeric material.

96. The composition of claim 95, wherein the polymeric material is formed of polymer fibers as a mesh or sponge.

97. The composition of claim 95, wherein the polymeric material comprises monomers selected from the group of monomers consisting of glycolic acid, lactic acid, propyl fumarate, caprolactone, hyaluronan, hyaluronic acid and combinations thereof.

98. The composition of claim 95, wherein the polymeric material comprises proteins, polysaccharides, polyhydroxy acids, polyorthoesters, polyanhydrides, polyphosphazenes, synthetic polymers or combinations thereof.

99. The composition of claim 95, wherein the polymeric material is a hydrogel formed by crosslinking of a polymer suspension having the cells dispersed therein.

100. The composition of claim 95, wherein the lattice further comprises a hormone selected from the group of hormones consisting of cytokines and growth factors.

101. A method of obtaining a genetically-modified cell comprising exposing the cell of claim 80 to a gene transfer vector comprising a nucleic acid including a transgene, whereby the nucleic acid is introduced into the cell under conditions whereby the transgene is expressed within the cell.

102. The method of claim 101, wherein the transgene encodes a protein conferring resistance to a toxin.

103. A method of delivering a transgene to an animal comprising (a) obtaining a genetically-modified cell in accordance with claim 102 and (b) introducing the cell into the animal, such that the transgene is expressed *in vivo*.

104. A method of differentiating the cell of claim 80, comprising culturing the cell in a morphogenic medium under conditions sufficient for the cell to differentiate.

105. The method of claim 104, wherein the medium is an adipogenic, chondrogenic, cardiogenic, dermatogenic, embryonic, fetal, hematopoetic, hemangiogenic, myogenic, nephrogenic, neurogenic, neuralgiagenic, urogenitogenic, osteogenic, pericardiogenic, peritoneogenic, pleurogenic, and splanchogenic, or stromogenic media.

106. The method of claim 104, wherein the morphogenic medium is an adipogenic medium and the cell is monitored to identify adipogenic differentiation.

107. The method of claim 104, wherein the morphogenic medium is a chondrogenic medium and the cell is monitored to identify chondrogenic differentiation.

108. The method of claim 104, wherein the morphogenic medium is an embryonic or fetal medium and the cell is monitored to identify embryonic or fetal phenotype.

109. The method of claim 104, wherein the morphogenic medium is a myogenic medium and the cell is monitored to identify myogenic differentiation.

110. The method of claim 104, wherein the morphogenic medium is an osteogenic medium and the cell is monitored to identify osteogenic differentiation.

111. The method of claim 104, wherein the morphogenic medium is a stromal medium and the cell is monitored to identify stromal or hematopoetic differentiation.

112. The method of claim 104, wherein the cell differentiates *in vitro*.

113. The method of claim 104, wherein the cell differentiates *in vivo*.

114. A method of producing hormones, comprising (a) culturing the cell of claim 85 within a medium under conditions sufficient for the cell to secrete the hormone into the medium and (b) isolating the hormone from the medium.

115. A method of promoting the closure of a wound within a patient comprising introducing the cell of claim 85 into the vicinity of a wound under conditions sufficient for the cell to produce the hormone, whereby the presence of the hormone promotes closure of the wound.

116. A method of promoting neovascularization within tissue, comprising introducing the cell of claim 85 into the tissue under conditions sufficient for the cell to produce the hormone, whereby the presence of the hormone promotes neovascularization within the tissue.

117. The method of claim 116, wherein the tissue is within an animal.

118. The method of claim 116, wherein the tissue is a graft.

119. The method of claim 116, wherein the hormone is a growth factor selected from the group of growth factor consisting of human growth factor, nerve growth factor, vascular and endothelial cell growth factor, and members of the TGFβ superfamily.

120. A method of conditioning culture medium comprising exposing a cell culture medium to the cell of claim 80 under conditions sufficient for the cell to condition the medium.

121. The method of claim 120, wherein the medium is separated from the cell after it has been conditioned.

122. A conditioned culture medium produced in accordance with the method of claim 120.

123. The conditioned culture medium of claim 122, which is substantially free of lipo-derived stem cells.

124. A method of culturing a stem cell comprising maintaining a stem cell in the conditioned medium of claim 122 under conditions for the stem cell to remain viable.

125. The method of claim 124, which further comprises permitting successive rounds of mitotic division of the stem cell to form an expanded population of stem cells.

126. The method of claim 124, wherein the medium is substantially free of lipo-derived stem cells.

127. The method of claim 124, wherein the medium contains lipo-derived cells.

128. The method of claim 127, wherein a stem cell and a lipo-derived cell are in contact.

129. The method of claim 124, wherein a stem cell is a hemopoetic stem cell.

130. An implant comprising the cell of claim 80.

131. An implant comprising the population of claim 87.

132. A method of isolating stem cells from adipose tissues comprising isolating adipose tissue from a patient and separating stem cells from the remainder of the adipose tissue.

133. The method of claim 132, further comprising differentiating the stem cells.

134. The method of claim 133, wherein the stem cells are differentiated into one or more precursor cell types.

135. The method of claim 134, wherein one or more precursor cell types is selected from the group of precursor cell types consisting of preadipocytes, premyocytes, and preosteocytes.

136. The method of claim 133, wherein the stem cells are differentiated into one or more mature cell types.

137. The method of claim 134, wherein one or more cell types is selected from the group of cell types selected from the group of cell types consisting of adipocytes, chondrocytes, dermal connective tissue cells, hemangial cells tissues, myocytes, osteocytes, neurons, neralglia, urogenital cells, pleural and peritoneal cells, visceral cells, mesodermal glandular cells, and stromal cells.

138. The method of claim 132, wherein the adipose tissue is liposuction effluent.